

Application No.: 10/717,677
Response dated: March 25, 2008
Reply to Office Action dated: September 27, 2007

28. (withdrawn) A method of culturing undifferentiated human stem cells with reduced differentiation comprising:

- a) growing the undifferentiated human stem cells in culture on a flexible solid porous matrix without conditioned media and in the absence of fibroblast feeder cells, wherein the stem cells are defined by the positive expression of Oct4 and SSEA-4 cell surface markers; and
- b) applying an effective amount of periodic strain on the flexible matrix to stretch the matrix and the undifferentiated stem cells thereon, such that the undifferentiated cells proliferate and exhibit reduced differentiation relative to undifferentiated human stem cells not subjected to periodic strain.

REMARKS

In a non-final Office Action mailed September 27, 2007, the Examiner in charge of the above-noted application withdrew the finality of the previous Office Action in response to Applicants filing of a Request for Continued Examination and entered Applicants' prior response. Applicants noted a small inconsistency in the statement of claims pending, considered or withdrawn: Claim 1 (withdrawn) was said to have been considered on the merits while Claim 13 (pending) was not listed among the considered claims. Applicants believe that the Examiner intended to state that Claim 13, not Claim 1, was considered. The Examiner's statement is otherwise accurate. The Examiner objected to informalities in Claims 16-24 and 27 and rejected Claims 13, 16-24, 26 and 27 for obviousness in view of Russell et al. (US 2002/0081726) in view of Xu et al. (2001) in light of Thomson et al. (1998).

Applicants respond below to the issues presented in the Office Action. In view of the claim amendments and arguments presented herein, applicants respectfully request reconsideration of the merits of this application.

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Claim Amendments

The claims under consideration are amended to clarify that the claims are composition claims, without reference to method or product-by-process steps. The compositions comprise proliferating (i.e., self-renewing) human ES cells in an unconditioned culture medium on a flexible matrix without feeder cells in an apparatus configured to apply strain to the matrix and the cells. An attribute of the cells in the composition is stated in the form of a test, namely that more of the cells are undifferentiated than in an otherwise comparable cell culture composition comprising an apparatus not configured to apply periodic strain to the matrix and the human ES cells. Support for this recitation is found at least in paragraph [00029] of the application as filed. In other words, the claimed compositions can be obtained after periodic strain is applied, as disclosed, but the method step of applying periodic strain is not an attribute of the composition *per se*. A skilled artisan can readily ascertain whether a composition meets the claims by comparing the extent of cell differentiation in the composition to that of another composition comprising an apparatus that is not configured to apply periodic strains to the matrix and the cells.

The dependent culture composition claims are amended to simplify the claim language, to render the claims consistent with the independent claim, and to address the language informalities noted by the Examiner in the Office Action. Claim 26 is recast as a dependent claim depending from Claim 13.

The withdrawn method claims are not further amended in this response, but Applicants stand ready to facilitate rejoinder by coordinating the withdrawn method claims with the product claims upon indication of allowable subject matter.

Claim Rejections - 35 USC §103(a)

The claims under consideration stand rejected for alleged obviousness over the indicated patent application and papers. The Examiner took issue with the prior pending claims for two reasons: (1) recitations about the cells do not provide any structural difference from that disclosed, *arguendo*, in the cited documents and (2) certain claims disclosed, *arguendo*, method steps that render the claims product-by-process claims. The Examiner's position is summarized on page 9 of the Office Action:

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Thus, whether or not cells stayed undifferentiated does not make the current invention unobvious. Applicant is reminded that the current claims under examination are clearly drawn to the product rather than the method. Therefore, the references in combination [citations omitted] teaching undifferentiated hES cells, flexible porous matrix (Matrigel), without conditioned media or fibroblast feeder cells, and an apparatus capable of providing mechanical strain to stretch cells would render the claimed invention obvious.

Applicants agree that the claims are product claims and here amend the claims to avoid any uncertainty in that regard. As described, the claimed culture compositions can be obtained after practice of a straining method step, but the method step is not an attribute of the composition *per se*.

Applicants respectfully disagree with the Examiner's conclusion that the product claims are obvious over the citations. Applicants do not claim to have here invented undifferentiated human ES cell culture, and acknowledge the prior existence of human ES cells. Rather, Applicants assert that Applicants' composition, notably the extent to which the cells in the composition are undifferentiated, would be unexpected in view of the cited documents. One important and challenging goal of human ES cell culture is to maintain proliferating, self-renewing ES cells because ES cells, left alone, tend to differentiate and to lose their pluripotent character. Russell teaches that a stretching apparatus differentiates cells cultured therein in a matrix. It follows logically that a skilled person interested in maintaining proliferating human ES cells would not place the cells in an apparatus for promoting differentiation. The Examiner has pointed to nothing in Russell that would suggest that an ordinarily skilled artisan would understand how to maintain any cell type, let alone human ES cells, in an undifferentiated state. That being so, query why the skilled person would have combined human ES cells with the apparatus in the first instance?

By not rejecting the claims for anticipation, the Examiner tacitly acknowledges that no inventor or author of a cited document actually applied human ES cells in culture to an apparatus configured to apply strain to the cells. The Examiner offers no proof that any inventor or author contemplated applying human ES cells in culture to an apparatus configured to apply strain to the cells or, still further, that any inventor or author even contemplated the differentiation status of cells in a culture composition as claimed. The Examiner would agree that any motivation to obtain or

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evaluate human ES cells in a composition as claimed could only have come from the mind of a hypothetical person of ordinary skill in the art. However, the citations taken as a whole provide the hypothetical skilled person with no motivation to combine the citations and, indeed, teach away from making Applicants' claims.

It is insufficient to simply assert, without more, that the prior existence of both (1) a cell/matrix stretching apparatus and (2) undifferentiated human ES cells motivates the skilled person to combine the two, especially in light of Applicants' unexpected showing that the combination results in a composition wherein more of the human ES cells in the culture medium are undifferentiated than in an otherwise comparable cell culture composition comprising an apparatus not configured to apply periodic strain to the matrix and the human ES cells. Absent any indication that the skilled person would have expected to achieve Applicants' claimed composition, and absent any indication that any skilled person actually made the claimed composition, the skilled person would have been led away from even trying to construct the claimed cell culture composition. The combination rejection must fail and should be withdrawn. Reconsideration is respectfully requested.

Fees

A petition for a three month extension of time accompanies this response so the response will be deemed to have been timely filed. Please charge the petition fee to Deposit Account No. 17-0055. Should any other extension of time be due in this or any other response, please consider this to be a petition for the appropriate extension of time and a request to charge the fee due the same Deposit Account. No additional fee, including additional claim fee, is believed due, but if any additional claim fee is due, in this or any subsequent response, please charge the same Deposit Account.

Respectfully submitted,

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